

P07 43453 (18810-80645)

In the Claims:

Please amend Claims 1, 4, 9, 11-18, 21, 26, 28-34, 97, 100, 104, 108, and 109, as follows.

1. (Twice Amended) A method of delivering a medicant to an abnormal brain region in a mammalian subject, comprising:

administering to a mammalian subject having an abnormal brain region an agonist of a calcium-activated or ATP-sensitive potassium channel, the agonist being other than bradykinin or a bradykinin analog, under conditions and in an amount sufficient to increase the permeability to the medicant of a capillary or arteriole delivering blood to cells of the abnormal brain region; and

administering to the subject simultaneously or substantially simultaneously with the agonist the medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions.

4.(Amended) The method of Claim 1, wherein the agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levocromakalim.

9.(Amended) The method of Claim 1, wherein the medicant is a N-methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2, transforming growth factor- β , cisplatin, carboplatin, tumor necrosis factor- α , methotrexate, 5-fluorouracil, amphotericin, daunorubicin, doxorubicin, vincristine, vinblastine, busulfan, chlorambucil, cyclophosphamide, melphalan, or ethyl ethanesulfonic acid.

10. 11.(Amended) The method of Claim 1, wherein administering the agonist is by intravenous or intra-arterial infusion or injection.

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11 12.(Amended) The method of Claim 1, wherein administering the agonist is by intracarotid infusion or injection.

12 13.(Amended) The method of Claim 1, wherein the agonist is administered to the mammalian subject by a bolus injection.

13 14.(Amended) The method of Claim 1, wherein the agonist is administered to the mammalian subject in an amount from about 0.075 to 1500 micrograms per kilogram body mass.

14 15.(Amended) The method of Claim 14, wherein the agonist is administered to the subject in an amount from about 0.075 to 150 micrograms per kilogram body mass.

15 16.(Amended) The method of Claim 1, wherein the agonist is administered to the mammalian subject at a dose rate of about 0.075 to about $100 \mu\text{g kg}^{-1} \text{ min}^{-1}$ for up to about 30 minutes.

16 17.(Amended) The method of Claim 16, wherein the agonist is administered to the mammalian subject at a dose rate of about 0.075 to about $15 \mu\text{g kg}^{-1} \text{ min}^{-1}$.

17 18.(Twice Amended) A method of selectively delivering a medicant to an abnormal brain region in a mammalian subject, comprising:

administering to a mammalian subject having an abnormal brain region an agonist of a calcium-activated or ATP-sensitive potassium channel, the agonist being other than bradykinin or a bradykinin analog, under conditions and in an amount sufficient to increase potassium flux through a calcium-activated or ATP-sensitive potassium channel in an endothelial cell membrane of a capillary or arteriole delivering blood to cells of the abnormal brain region, whereby the capillary or arteriole is made more permeable to the medicant; and

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administering to the subject simultaneously or substantially simultaneously with the agonist the medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions.

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~~20~~ ²¹(Amended) The method of Claim ~~18~~ ¹⁷, wherein the agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levocromakalim.

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~~25~~ ²⁶(Amended) The method of Claim ~~18~~ ¹⁷, wherein the medicant is a N-methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2, transforming growth factor- β , cisplatin, carboplatin, tumor necrosis factor- α , methotrexate, 5-fluorouracil, amphotericin, daunorubicin, doxorubicin, vincristine, vinblastine, busulfan, chlorambucil, cyclophosphamide, melphalan, or ethyl ethanesulfonic acid.

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~~26~~ ²⁸(Amended) The method of Claim ~~18~~ ¹⁷, wherein administering the agonist is by intravenous or intra-arterial infusion or injection.

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~~27~~ ²⁹(Amended) The method of Claim ~~18~~ ¹⁷, wherein administering the agonist is by intracarotid infusion or injection.

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~~28~~ ³⁰(Amended) The method of Claim ~~18~~ ¹⁷, wherein the agonist is administered to the mammalian subject by a bolus injection.

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~~29~~ ³¹(Amended) The method of Claim ~~18~~ ¹⁷, wherein the agonist is administered to the mammalian subject in an amount from about 0.075 to 1500 micrograms per kilogram body mass.

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~~30~~ ³²(Amended) The method of Claim ~~31~~ ²⁹, wherein the agonist is administered to the subject in an amount from about 0.075 to 150 micrograms per kilogram body mass.

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E11
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31 33 (Amended) The method of Claim ¹⁷ 18, wherein the agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 100 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ for up to about 30 minutes.

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34 (Amended) The method of Claim ³¹ 33, wherein the agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 15 $\mu\text{g kg}^{-1} \text{ min}^{-1}$.

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37 (Twice Amended) A pharmaceutical composition comprising a combination of an agonist of a calcium-activated or ATP-sensitive potassium channel, the agonist being other than bradykinin or a bradykinin analog, formulated in a pharmaceutically acceptable solution together with a medicant for delivery by intravascular infusion or injection into a mammal.

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36 100 (Amended) The pharmaceutical composition of Claim ³³ 37, wherein the agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levocromakalim.

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40 104 (Twice Amended) The pharmaceutical composition of Claim ³³ 37, wherein the medicant is a N-methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2, or transforming growth factor- β .

E15
43 108 (Thrice Amended) A kit for enhancing the delivery of a medicant to an abnormal brain region, comprising:

an agonist of a calcium-activated or ATP-sensitive potassium channel, potassium the agonist being other than bradykinin or a bradykinin analog; and

instructions for using the agonist for enhancing the delivery of a medicant to an abnormal brain region by increasing the permeability of a capillary or arteriole delivering blood to cells of the abnormal brain region.

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